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Minireview

Therapeutic Basis of Generic Substitution of Antiseizure Medications

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ABSTRACT

More than thirty antiseizure medications (ASMs) are available for treating epilepsy. ASMs differ in their potency and efficacy in controlling seizures by acting on diverse targets in the brain, often with variable pharmacokinetics. Moreover, nearly 30% of people with epilepsy have drug-resistant or intractable seizures. Generic substitution of ASMs is a complex issue. It is thought that frequent generic substitution in people with epilepsy may cause problems because the U.S. Food and Drug Administration (FDA) rules allow too much variability across products. The standard bioequivalence range (80% to 125%) appears too broad for many ASMs, especially those exhibiting little separation between therapeutic and toxic levels. Hence, sub-therapeutic concentration may lead to therapeutic failure with seizure recurrence, which could be life threatening. A supra-therapeutic level could result in adverse effects or compliance issues. There are reported issues with generic substitutions of phenytoin, topiramate, levetiracetam, carbamazepine, and lamotrigine. There is discussion in the epilepsy community about additional guidelines, including designation of generic ASMs as Narrow Therapeutic Index (NTI) drugs and how patient education plays a role in generic substitution. Overall, based on the published evidence on specific generic ASMs, FDA bioequivalence standards are not the cause of problems with generic ASM substitution. Rather, it is imperative that physicians and pharmacists provide adequate patient education on what to expect when switching to generic ASMs, including changes in medication shape and color. Another suggestion would be to consider that all ASMs be considered for inclusion in NTI class to prevent the clinical outcome issues associated with generic ASM switching.

SIGNIFICANCE STATEMENT

There are critical aspects to consider when switching from a brand name antiseizure medication (ASM) when a generic becomes available or switching between generics. Generic ASMs are interchanged with little consideration of differences in therapeutic equivalence and other clinical factors. This article describes key issues on generic substitution of ASMs and highlights critical pharmacotherapeutic issues associated with generic ASMs.

Introduction

Epilepsy is a chronic neurologic condition characterized by repeated unprovoked seizures and a spectrum of neuropathology. It is estimated that the worldwide prevalence of individuals with active epilepsy is around 0.5% to 1%, corresponding to about 65 million people (Sander, 2003; Kros et al., 2015). Currently, there are no pharmacological therapies that offer a cure for epilepsy (Reddy and Golub, 2016). Antiseizure medications (ASMs) offer adequate seizure control for many patients, allowing them to lead a normal life (Kwan and Sander, 2004). In fact, up to 70% of patients taking ASMs can be seizure-free with the appropriate dose and type of ASM (Heaney and Sander, 2007). Pharmacological treatments vary depending on the type of epilepsy. Epileptic seizures that arise focally in a cortical site are referred to as focal seizures and comprise 60% of all seizures (Kammerman and Wasserman, 2001; Duncan et al., 2006; Goldenberg, 2010). The other 40% of epileptic seizures involve arise from both cerebral hemispheres and are known as generalized seizures (Kammerman and Wasserman, 2001; Duncan et al., 2006; Goldenberg, 2010).

The different types of epilepsy and variety in epileptic seizures that present in patients has resulted in a demand for the creation of multiple ASMs. The goals of ASM therapy are to

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ABBREVIATIONS: ASM, antiseizure medication; AUC, area under the concentration time curve; FDA, U.S. Food and Drug Administration; NTI, narrow therapeutic index.

completely eliminate or reduce seizures as much as possible, avoid adverse side effects from medication, and to help patients return to normal activities and maintain a normal lifestyle (Goldenberg, 2010). ASMs can be separated into two general categories: broad-spectrum and narrow-spectrum medications. As the name implies, broad-spectrum ASMs treat multiple types of epilepsy, whereas narrow-spectrum ASMs are used primarily for the treatment of focal seizures (Reddy, 2020). Some of the most common generic ASMs available in the U.S. are listed in Table 1, with the brand drug name in parentheses (Lewis, 1978; Brodie et al., 2016; Reddy, 2020). The classification of different ASMs into broad-spectrum and narrow-spectrum has some relation to the mechanism of action of each drug. The molecular classification of these drugs can be seen in Table 2 (Reddy, 2020).

There are many bioequivalence and therapeutic issues to consider when switching from a brand name ASM when a generic becomes available or switching between generics from different manufacturers. Frequent generic substitution in people with epilepsy can cause problems because FDA rules allow too much variability across products. This article describes the key differences between generic and brand name ASMs, highlights critical pharmacotherapeutic issues associated with generic ASMs, and examines specific studies on generic substitutions of lamotrigine.

Substitution of Generic ASMs

Rationale for Prescribing Generic ASMs. The U.S. Food and Drug Administration (FDA) defines a generic drug as a medication that is identical—or bioequivalent—to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use (Alfonso-Cristancho et al., 2015).

Over the years, physicians have gradually shifted from prescribing brand name drugs to generic medications because of low cost to patients. Many health insurance plans operate under a tiered system for prescription medications. These plans often rely on a formula that accounts for how much the medication will cost the insurance company compared with the cost of the same generic drug. More expensive medications fall into a tier that increases cost to patients, whereas generic medications and other substitutes fall into a different tier that is more affordable to patients. These plans generally serve as an incentive for beneficiaries to choose generic medications to save money. Additionally, they simultaneously encourage pharmaceutical manufacturers to lower the cost of drugs, with the understanding that the medication will be placed into a more affordable tier level (Goldman et al., 2007).

The cost of a generic drug is generally 20% to 90% less expensive than the brand name equivalent. Furthermore, in 2010, the use of FDA-approved generic medications saved a total of $158 billion, amounting to savings of $3 billion a week (Dunne et al., 2013). These savings have a sizable impact on adherence to drug therapy because patients can afford to purchase medication (Kesselheim et al., 2006; Shrank et al., 2006; Goldman et al., 2007). The financial impact of generic ASMs plays an even more important role for economically disadvantaged patients or those without health insurance (Atif et al., 2016).

Prescribing Trends of ASMs. More than thirty ASMs are available for treating epilepsy, including many new drugs

TABLE 1.
Common generic ASMs prescribed in the U.S.

Broad-Spectrum ASMs	Name of Drug [a,b,c]
	Clobazam (Onfi)
	Clonazepam (Klonopin)
	Diazepam (Valium)
	Lamotrigine (Lamictal)
	Levetiracetam (Keppra)
	Rufinamide (Banzel)
	Topiramate (Topamax)
	Valproic Acid (Depakene)
	Zonisamide (Zonegran)
	Carbamazepine (Tegretol)
	Ethosuximide (Zarontin)
	Ezogabine (Trobalt)
	Gabapentin (Neurontin)
Narrow-Spectrum ASMs	
	Lacosamide (Vimpat)
	Oxcarbazepine (Trileptal)
	Perampanel (Fycompa)
	Phenobarbital (Luminal)
	Phenytoin (Dilantin)
	Pregabalin (Lyrica)
	Vigabatrin (Sabril)

[a]Reddy, 2020
[b]Brodie et al., 2016
[c]Lewis, 1978

TABLE 2.
Molecular classification of ASMs

Mechanism[a]	Drug[a]
Blockage of voltage-gated sodium channels	Phenytoin
-Block firing propagation	Fosphenytoin
-Stabilize neuronal membranes	Carbamazepine
-Reduce neurotransmitter release	Valproate
-Reduce focal firing	Lamotrigine
-Reduce seizure spread	Oxcarbazepine
	Esclicarbazepine
	Lacosamide
Enhancement of GABA inhibition	Phenobarbital
-Increase neuronal hyperpolarization	Primidone
-Increase seizure threshold	Diazepam
-Reduce firing rate	Lorazepam
	Clonazepam
	Tiagabine
	Valproate
	Vigabatrin
Blockage of low-threshold (T-type) Ca^{2+} channels	Ethosuximide
	Gabapentin
-Reduce neurotransmitter release—slow depolarization	Valproate
Reduction of glutamate excitation	Felbamate
-Reduce excitatory transmission	Gabapentin
-Reduce focal firing	Parampanel
Binding to SV2 synaptic vesicle protein	Levetiracetam
-Reduce transmitter release	Briveracetam
$\alpha 2\delta$ Ligands	Gabapentin
	Pregabalin
Modulators of K+ (KCNQ2-5) channels	Ezogabine (retigabine)
-Reduce bursts of firing	
-Hyperpolarize neurons	

[a]Reddy, 2020

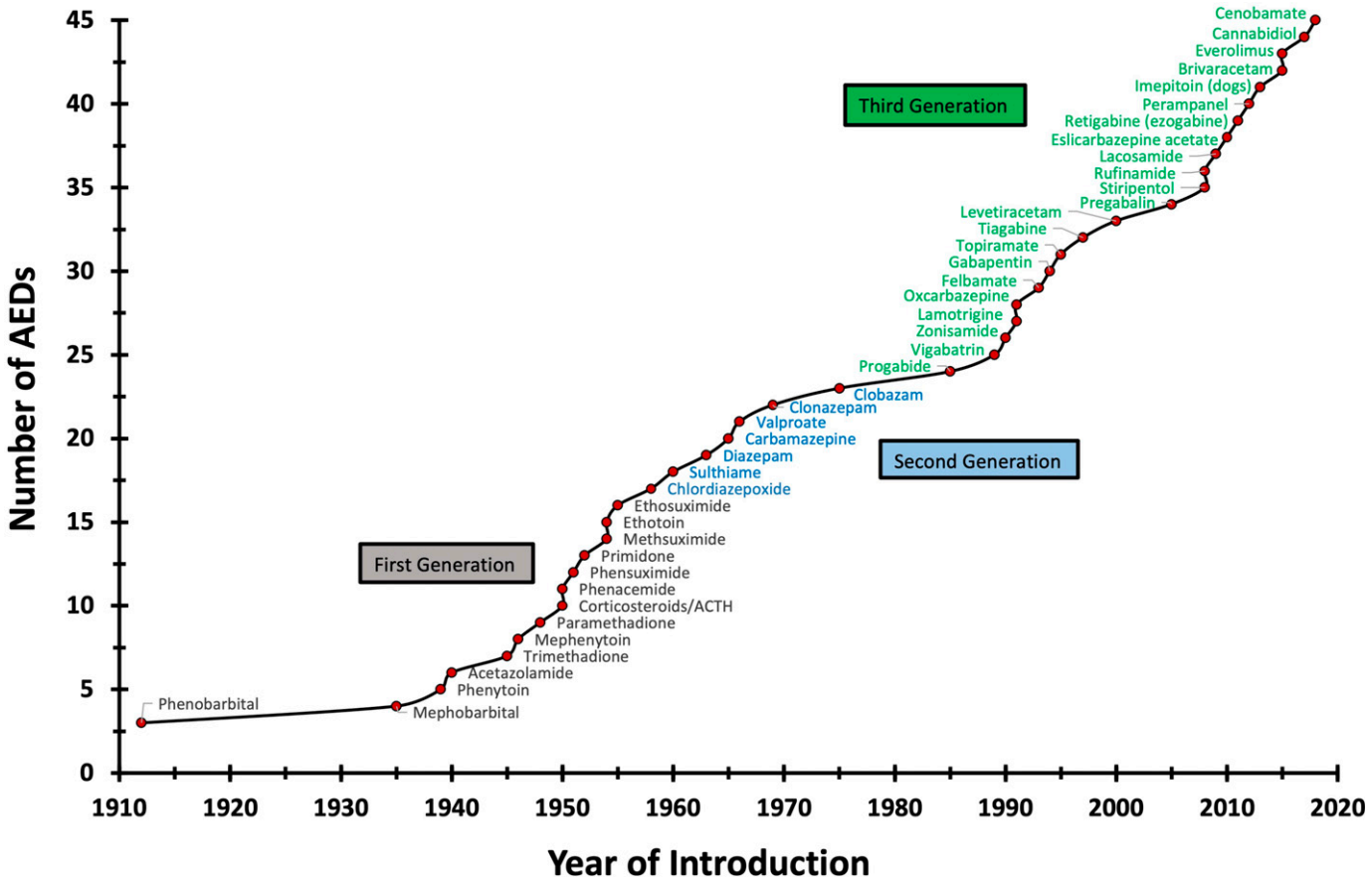

Fig. 1. Introduction of generic antiseizure medications (ASMs) by year. First generation ASMs were introduced prior to 1965, whereas second generation ASMs are structurally different from barbiturate type agents. Third generation ASMs are developed mostly based on target mechanism or seizure indication. Modified from Löscher and Klein (2020).

approved within the past two decades. A timeline of the introduction of first, second, and third generations of ASMs is depicted in Fig. 1 (Löscher and Klein, 2020). The top 10 generic ASMs prescribed in the U.S. were determined using data from the Medical Expenditure Panel Survey gathered by the Agency for Healthcare Research and Quality. This data, collected and organized by ClinCalc.com into a Drug Stats database, provides information about the top 200 most commonly prescribed drugs of 2018. This data was used as the basis for the article "Comprehension of Top 200 Prescribed Drugs in the US." Of the top 200 drugs, generic ASMs comprise 11 of these. Gabapentin topped the list as the 11th most commonly prescribed medication in the U.S. A brief overview of this data, including ranking and total number of prescriptions for each drug, is summarized in Table 3.

Generic Drug Approval Process

Bioequivalence. To receive approval from the FDA, generic drug manufacturers must undergo a rigorous process to demonstrate that the generic version is bioequivalent to the brand name. Bioequivalence is defined by the FDA as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (Chen et al., 2001). To determine bioequivalence, it is critical to first examine bioavailability. Bioavailability is defined by the FDA as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action (Chen et al., 2001). In determining the bioavailability of a drug, three pharmacokinetic factors must be considered: peak plasma concentration (C_{max}), the time to reach peak plasma concentration (C_{max}), and area under the concentration time curve (AUC). The C_{max} and AUC are important in determining bioequivalence, as the C_{max} represents the maximum concentration of a drug in the blood plasma at a given time, whereas the AUC represents the total concentration of the drug that is absorbed. The (C_{max}) is an important parameter to gauge the rate of drug absorption. Current FDA regulations state that a generic medication can meet bioequivalence standards, given that the AUC and C_{max} ratios of both the generic and brand name drug fall within a range of 80% to 125% with a 90% confidence interval (Rani and Pargal, 2004; Chow, 2014; Atif et al., 2016; Berg et al., 2017).

Bioequivalence and its relation to therapeutic equivalence are further complicated by differences in metabolism between various ASMs. ASMs are metabolized by the hepatic microsomal system, meaning that certain drugs can induce this system, thereby diminishing the effects of a given ASM. Alternatively, some drugs may inhibit this system, resulting

TABLE 3.
Top 13 most commonly prescribed generic ASMs in the U.S. in 2018

Brand and Generic Name	Year of First Generic Approval[a]	Ranking[b]
Gabapentin (Neurontin)	2003	#1 for Generic ASMs #13 Overall
Clonazepam (Klonopin)	1996	#2 for Generic ASMs #38 Overall
Lorazepam (Ativan)	1985	#3 for Generic ASMs #55 Overall
Lamotrigine (Lamictal)	2006	#4 for Generic ASMs #70 Overall
Topiramate (Topamax)	2003	#5 for Generic ASMs #77 Overall
Pregabalin (Lyrica)	2019	#6 for Generic ASMs #79 Overall
Diazepam (Valium)	1985	#7 for Generic ASMs #91 Overall
Levetiracetam (Keppra)	2008	#8 for Generic ASMs #118 Overall
Valproic Acid (Depakote)	1986	#9 for Generic ASMs #120 Overall
Phenytoin (Dilantin)	1992	#10 for Generic ASMs #158 Overall
Oxcarbazepine (Trileptal)	2007	#11 for Generic ASMs #176 Overall
Carbamazepine (Tegretol)	1986	N/A for Generic ASMs N/A Overall
Ethosuximide (Zarontin)	1993	N/A for Generic ASMs N/A Overall

[a]FDA Approved Drug Products, 2021
[b]Fuentes et al., 2018

in the enhancement and supratherapeutic concentrations of ASMs. This can result in significant drug interactions, especially in patients taking multiple medications. The enzyme properties of different ASMs are summarized in Table 4 (Reddy, 2020).

Narrow Therapeutic Index. In considering the manufacturing of bioequivalent generic ASMs, it is important to consider those with a narrow therapeutic index (NTI). According to the FDA, drugs are classified as NTI if the difference in ratio between the median minimum toxic concentration and the minimum effective blood concentration is less than twofold (Shaw and Hartman, 2010; Tamargo et al., 2015). Knowledge of NTI ASMs is especially important when considering therapies for epilepsy. Specifically, clinicians should pay close attention to the therapeutic window of a drug, which reflects the concentration range that provides therapeutic benefit without causing toxicity (Blix et al., 2010). NTI drugs have a very narrow therapeutic window. A narrow therapeutic window means that a small difference in dosing or blood concentration of the medication can have potentially life threatening toxic effects (Tamargo et al., 2015). As a result, the doses of these drugs must be monitored closely and administered carefully to prevent toxicity in patients (Blix et al., 2010; Tamargo et al., 2015).

TABLE 4.
ASMs that do and do not induce hepatic enzymes

Enzyme-Inducing ASMs[a]	Enzyme Non-Inducing ASMs[a]
Brivaracetam (Briviact)[b]	
Carbamazepine (Tegretol)	Clonazepam (Rivotril)
Clobazam (Onfi)	Ethosuximide (Zarontin)
Esclicarbazepine (Aptiom)	Ezogabine
Felbamate (Felbatol)	Gabapentin (Neurontin)
Lamotrigine (Lamictal)[c]	Lacosamide
Oxcarbazepine (Trileptal)	Levetiracetam (Keppra)
Perampanel (Fycompa)[b]	Stiripentol
Phenobarbital (Luminal)	Pregabalin (Lyrica)
Phenytoin (Dilantin)	Tiagabine (Gabitril)
Primidone (Mysoline)	Vigabatrin (Sabril)
Rufinamide (Banzel)	Valproate (Depakote)
Topirimate (Topamax)	Zonisamide (Zonegran)

[a]Reddy, 2020
[b]Weak enzyme inhibitor
[c]Weak enzyme inducer

Five ASMs are commonly listed as NTIs: carbamazepine, phenytoin, phenobarbital, ethosuximide, and valproic acid (Sankar and Glauser, 2010; Hottinger and Liang, 2012; Jankovic and Ignjatovic Ristic, 2015; Atif et al., 2016; Greenberg et al., 2016). In regard to epilepsy therapy, there are potential problems associated with the substitution of brand name ASMs with generics. Using the classic 80% to 125% range approved by the FDA for generic medications poses a threat to individuals who have a high sensitivity to plasma ASM concentration. Generic ASMs that fall below this range can be therapeutically ineffective, resulting in a greater occurrence of seizures and other complications from epilepsy. Conversely, generic ASMs that exceed the upper limit can cause serious adverse effects or toxicity in patients. Table 5 lists the therapeutic range and the FDA bioequivalence extrapolated therapeutic range for seven ASMs, including the five that are classified as NTI (Atif et al., 2016; Fuentes et al., 2018).

Clinical Problems with FDA Therapeutic Ranges. The literature shows that there have been health concerns associated with the use of generic ASMs over their brand name equivalent. There are multiple reports from clinicians that FDA criteria for generic ASMs pose a risk to patients because of the difference between bioequivalence and therapeutic equivalence. Specifically, the AUC and C_{max} of generic ASMs are only required to be within a range of 80% to 125%. However, at a C_{max} of 81% of the normal therapeutic range, doses that are too low may result in breakthrough seizures and failure of ASM therapy, resulting in an increase in the frequency of seizures (Koch and Allen, 1987; Sachdeo and Belendiuk, 1987; Hartley et al., 1990, 1991; Meyer et al., 1992; Welty et al., 1992; Jain, 1993; Berg, Gross, Tomaszewski, et al., 2008; Atif et al., 2016). In fact, two-thirds of physicians report that they have treated a patient who experienced a breakthrough seizure after switching from a brand name ASM to a generic (Guberman and Corman, 2000; Wilner, 2004; Berg, Gross, Haskins, et al., 2008; Berg, Gross, Tomaszewski, et al., 2008; Fitzgerald and Jacobson, 2011). This has resulted in motor vehicle accidents, missed time at work, and increased visits to hospitals and physicians (Berg, Gross, Tomaszewski, et al., 2008).

Conversely, at a C_{max} of 124% of the normal therapeutic range, doses that are too high may result in drug toxicity, increased drug serum levels, undesired drug interactions, and other adverse side effects (Chen et al., 1982; Soryal and Richens, 1992; Levine et al., 2000; Borgheini, 2003; Chaluvadi et al., 2011; Atif et al., 2016).

Because of these reported problems with the FDA therapeutic ranges, drugs classified as NTI are subject to stricter regulations for substitution of brand name with generic counterparts in some states. In 2008, Berg, Gross, Tomaszewski, et al. published a paper that incorporated the 2006 state formulary guidelines by the National Association of Boards of Pharmacy. The formulary guidelines outlined the specific NTI

TABLE 5.
Commonly prescribed generic ASMs and their accepted therapeutic ranges

Generic ASM[a]	Ranking Among Generic ASMs[b]	Therapeutic Range	FDA Bioequivalence-extrapolated Therapeutic Range[c]	NTI Classification?
Gabapentin	1	4–20 μg/ml	3.2–25 μg/ml	No
Lamotrigine	4	4–20 μg/ml	3.2–25 μg/ml	No
Topiramate	5	10–20 μg/ml	8–25 μg/ml	No
Levetiracetam	8	5–40 μg/ml	4–50 μg/ml	No
Valproic acid	9	50–100 μg/ml	40–125 μg/ml	Yes
Phenytoin	10	10–20 μg/ml	8–25 μg/ml	Yes
Carbamazepine	N/A	4–12 μg/ml	3.2–15 μg/ml	Yes
Ethosuximide	N/A	40–100 μg/ml	32–125 μg/ml	Yes
Phenobarbital	N/A	20–40 μg/ml	16–5p0 μg/ml	Yes

[a]Atif et al., 2016
[b]Fuentes et al., 2018
[c]Based on FDA criteria (80% to 125%) for peak concentration, Cmax

drug substitution laws for each of the 50 states, Washington D.C., Guam, and Puerto Rico. Of these, 13 of the 43 states had a designated list of drugs that are not substitutable (NTI). Even in states that did not have a designated list of NTI drugs, there are regulations in place that allow prescribing physicians to prevent generic substitution of drugs (Berg, Gross, Tomaszewski, et al., 2008).

Reported Bioequivalence and Therapeutic Problems with Generic ASMs

Phenytoin. There are five major studies published on the problems associated with administration of generic phenytoin versus its brand name counterpart. The study by Shin et al. (2014) took a retrospective approach using electronic medical records and determined that the bioavailability of phenytoin was significantly different between generics. Soryal and Richens looked at the bioavailability of brand name and generic versions of phenytoin and determined that substitution between generic phenytoin or between generic phenytoin and brand name Epanutin caused a change in bioavailability, which was likely to have an adverse effect on seizure control and increase the incidence of side effects (Soryal and Richens, 1992). A review conducted by Borgheini examined literature about bioequivalence and therapeutic efficacy of different ASMs. In this, literature by Rosenbaum et al. (1994) showed that plasma levels of phenytoin were 31% lower after switching from brand name to generic phenytoin (Borgheini, 2003). Yamada and Welty (2011) did a systematic review of prospective and retrospective studies on generic substitution of ASMs, whereas Chen et al. (1982) examined the bioavailability of phenytoin from different generic formulas. These two studies both determined that the serum concentrations differed between generic and brand name phenytoin. These studies illustrate unfavorable outcomes with generic phenytoin products (Chen et al., 1982; Soryal and Richens, 1992; Rosenbaum et al., 1994; Borgheini, 2003; Yamada and Welty, 2011; Shin et al., 2014; Atif et al., 2016).

Topiramate. In Duh et al. (2009), medical and pharmacy claims from patients on topiramate were gathered and observation periods were sorted into three categories: brand use, single-generic use, and multiple-generic use. The study found that there was a significant association between multiple-generic substitution of topiramate and adverse health outcomes, including hospitalizations and injuries, as well as increased costs for treatment. This indicates that substitution between generic versions of topiramate poses a risk to patients (Duh et al., 2009; Atif et al., 2016).

Levetiracetam. In 2010, Armstrong et al. compared case studies on four different patients with brain tumors who had been switched from brand name Keppra to generic levetiracetam. All four patients experienced breakthrough seizures after switching medication, despite no change in their brain tumor size or severity. This demonstrates that changing from brand name to generic levetiracetam may not be suitable because the generic formulation may not be therapeutically equivalent (Armstrong et al., 2010). Fitzgerald and Jacobson (2011) also reported that four patients experienced an increase in breakthrough seizures after switching from Keppra to generic levetiracetam. After switching back to Keppra, all patients saw their seizure activity return to normal baseline (Fitzgerald and Jacobson, 2011). Chaluvadi and colleagues (2011) conducted a retrospective chart review of 260 patients who had switched from brand name to generic levetiracetam. Of these patients, 42.9% switched back to the brand name medication because of an increase in seizure frequency (19.6%) or an increase in adverse side effects (3.3%). These findings indicate that there are concerning outcomes associated with the substitution of brand name with generic levetiracetam (Armstrong et al., 2010; Chaluvadi et al., 2011; Fitzgerald and Jacobson, 2011; Atif et al., 2016).

Carbamazepine. A review conducted by Borgheini examined literature about bioequivalence and therapeutic efficacy of different ASMs. In his review, Borgheini included a study which demonstrated that switching from brand name to generic carbamazepine resulted in a recurrence of seizures (Borgheini, 2003). Desmarais et al. (2011) conducted a literature review of problems reported with switching from brand name to generic psychotropic medications, which included carbamazepine. Many of the authors included in the literature review reported problems with increased seizures and lower drug levels in the body, without a change in dosage, after switching from brand name to generic carbamazepine (Jain, 1993; Desmarais et al., 2011). Conversely, some authors cited toxicity issues. Specifically, a study by Vergely and team (2002) showed that one patient experienced a 3-fold increase in carbamazepine levels after switching from brand name to generic carbamazepine, which resulted in adrenal decompensation. In 2008, Berg, Gross, Tomaszewski, et al. reported on fifty patients who experienced a breakthrough seizure or increased seizure frequency after switching from a brand name to a generic ASM. Of these 50 patients, 7 of them were taking carbamazepine. Additionally, in 26 of the cases, the blood ASM level was recorded before

and after switching from brand name to generic. Of these 26 patients, 21 of them experienced lower drug concentration levels at the time of their breakthrough seizure. In fact, the drug levels of patients taking generic carbamazepine decreased by 20%, on average. These findings show the concerns associated with substitution of generic for brand name carbamazepine (Jain, 1993; Vergely et al., 2002; Borgheini, 2003; Berg, Gross, Tomaszewski, et al., 2008; Desmarais et al., 2011).

Lamotrigine. Desmarais et al. (2011) published a review of problems reported with switching from brand name to generic psychotropic medications, which included lamotrigine. In this review, he included a publication from Makus and McCormick (2007), which examined adverse reaction forms that had been submitted to the pharmacy by physicians whose patients had an adverse reaction to substitution with generic lamotrigine. Of these 14 patients, 11 reported loss of seizure control after being switched to the generic. However, when 10 of the patients were switched back to brand name lamotrigine, 80% of them regained seizure control (Makus and McCormick, 2007). Similarly, in a report from Nielsen et al. (2008), nine patients received drug monitoring while switching between lamotrigine formulations. One patient's C_{max} increased by 21% after switching from brand name to generic lamotrigine and he subsequently experienced ataxia and falls. Another patient's C_{max} decreased by 17% after switching from brand name to generic lamotrigine and they experienced seizures, even though they had previously been seizure-free for a year and a half before switching. These findings show the complications associated with switching patients to generic lamotrigine (Makus and McCormick, 2007; Nielsen et al., 2008; Desmarais et al., 2011).

Clinical Considerations for Changing Between Generic ASMs

Though there are numerous reports by physicians of problems with switching between generic and brand name ASMs, this is not standard for all patients. On average, the AUC of most generic medications differ from the brand name by less than 10% of their expected value (Davit et al., 2009). This indicates that the issue with substitution of ASMs does not solely lie with variability between brand name and generic medications. With this in mind, it is important to note that bioequivalence between a generic and brand name medication does not necessarily equate to bioequivalence between different generics. This means that two different generic ASMs could separately meet FDA bioequivalence standards when compared with a brand name medication. However, when compared with one another, they may not be bioequivalent to each other, resulting in clinically significant changes in plasma concentration of ASMs. Theoretically, given the FDA-accepted range of 80% to 125% for generic medications, if one generic was at the lowest possible acceptable end and the other at the highest, the difference between the AUC and C_{max} ratios between the two could amount to nearly 50%.

Studies by Karalis and colleagues (2013), (2014) showed that substitution between generic ASMs should not be considered therapeutically equivalent to switching between a generic and brand name ASM (Atif et al., 2016). In their 2013 study, they used Monte Carlo simulations of classic 2 × 2 bioequivalence studies to examine the effect of various factors on bioequivalence acceptance of generic ASM products. These factors include sample size, within-subject variability, and the true difference in pharmacokinetic values of the products being compared. Their findings showed that switches between bioequivalent generic ASMs could lead to larger changes in plasma levels and exposure than switching between brand and generics. Simply put, the simulation showed that two generic ASMs that are bioequivalent to the same original brand name product may not be bioequivalent to one another (Karalis et al., 2013).

This argument is supported by Odi and team (2021), who suggest that bioequivalence exists between brand name and generic ASMs, but not between different generics. They assert that potential issues arise when switching is done between different generic ASMs. The potential risks of switching from one generic to another is lessened when products meet NTI criteria for bioequivalence and have little difference in their pharmacokinetic parameters (Odi et al., 2021).

Studies Investigating Generic Substitution of ASMs

Position Statements. There are three major epilepsy organizations that have issued official position statements regarding the substitution of brand name ASMs with generics. In 2007, the American Academy of Neurology published a piece saying that they do not support the generic substitution of ASMs without prior approval from a patient's attending physician (Liow et al., 2007). After their position statement, they listed many other supporting opinions about generic ASM substitution. This list includes support for legislation that would mandate informed consent for both patients and physicians before any generic substitutions of ASMs are made (Liow et al., 2007).

Just a few months prior, the Epilepsy Foundation issued a statement in 2006 that closely mirrored the ideas expressed by the American Academy of Neurology. The Epilepsy Foundation stated that they are in strong support of informed consent for both physicians and patients before any type of ASM substitution is made. These substitutions include switching from brand to generic or even switching between generics. The Epilepsy Foundation also discouraged mandatory substitution of generic ASMs without authorization from the attending physician and patient (Epilepsy Foundation Medication Switching Position Statement, 2006).

The American Epilepsy Society issued a position statement in 2007 and then reissued a new statement in 2016. The 2016 the American Epilepsy Society position statement was based off of results from two different bioequivalence studies funded by the FDA. These studies are the BioEquivalence in Epilepsy Patients and Equivalence Among Generic Antiepileptic Drugs studies. The American Epilepsy Society stated that the experimental findings support the existing FDA standards for bioequivalence of generic ASMs. As a result, the American Epilepsy Society is in support of the FDA standards and asserts that there is no difference in bioequivalence between brand name and generic ASMs (Vossler et al., 2016).

BioEquivalence in Epilepsy Patients Study. The BioEquivalence in Epilepsy Patients Study was a randomized, double-blind, multiple-dose, steady-state, fully replicated study that compared generic lamotrigine to brand name Lamictal.

Specifically, the study examined pharmacokinetic performance in 35 "generic-brittle" patients already taking lamotrigine. "Generic-brittle" patients were those identified as potentially having problems switching from brand name to generic medications because of (1) a history of exacerbation of seizures or side effects following ASM formulation changes; (2) intolerable ASM side effects within the year prior to study; or (3) refractory seizures within the last year prior to study, suggesting clinical sensitivity to higher peak plasma concentration of ASM or slightly lower drug exposure. Of the 35 patients who participated, 23 met two or more of the criteria (Ting et al., 2015).

In this four-period study, patients were repeatedly switched between generic and brand name lamotrigine every 2 weeks. Patients were randomized to one of two sequences: generic, brand, generic, and brand; or the reverse. Subsequent blood sampling was taken at the end of every 2 week period (Ting et al., 2015).

The results showed that neither the brand name nor the generic showed identical pharmacokinetics in any of the patients when administered twice. Individual C_{max} and AUC ratios fell within ± 25% and most values for minimal plasma concentration C_{min} ratios also fell within this range. Overall, the findings showed that generic lamotrigine demonstrated bioequivalence to brand name Lamictal in AUC, C_{max}, C_{min}, and within-subject variability. In regard to seizure control, 32 of the 35 subjects reported that their seizure control was not worsened during the study. Similarly, no patients reported increased seizure severity. However, one subject experienced 267 short focal motor seizures without impairment of consciousness, which was a typical seizure type for this patient. However, the patient reported that this corresponded to "more than three times the number of seizures during the study" compared with their baseline. Most of these seizures occurred on generic lamotrigine, despite having very similar pharmacokinetic profiles during all four periods of the study. His seizures while taking generic lamotrigine did not correspond to lower plasma levels, as the profiles between generic and brand name were nearly identical. When this subject is excluded, the total number of seizures between the generic and brand name formulations is not substantially different (Ting et al., 2015).

This suggests that current FDA bioequivalence standards are appropriate, given that the adverse events related to switching were not related to differences in pharmacokinetic profiles. However, this raises the issue that bioequivalence between brand name and generics does not always equate to therapeutic equivalence.

Equivalence Among Generic Antiepileptic Drugs Study. The Equivalence Among Generic Antiepileptic Drugs study was a randomized, double-blind, crossover study in patients already taking lamotrigine to examine generic-to-generic switches. In the study, patients were allocated 1:1 to two treatment groups, with four study periods of 14 days each. At the end of each study period, patients were switched from one generic lamotrigine product to another. C_{max} and AUC were measured for each generic product in patients who completed the study. The findings showed that the 90% confidence interval of the ratios of C_{max} and AUC fell within the FDA-approved range of 80% to 125%. This indicates bioequivalence between generic lamotrigine products. Of note, there were no significant changes in seizure frequency, loss of seizure control, or adverse events recorded during the study. Given that the different formulations of generic lamotrigine were shown to be bioequivalent with no difference in clinical outcomes, this suggests that the FDA requirements for bioequivalence are suitable (Privitera et al., 2016).

Conclusions and Perspectives

There are some reports that conclude that generic ASMs pose few issues as compared with branded versions (Piñeyro-López et al., 2009; Kesselheim et al., 2010, 2013; Privitera et al., 2016; Holtkamp and Theodore, 2018; Odi et al., 2021) In particular, Holtkamp and Theodore (2018) suggest that the high switchback rates for patients who switch to generic ASMs and then back to brand name ASMs has more to do with improper administration of medication, rather than differing pharmacokinetics and pharmacodynamics between generic and brand name ASMs. These authors suggest that changes in medication shape and color that result from a change in the drug manufacturer may confuse patients and result in nonadherence to generic ASMs. To avoid this complication, Holtkamp and Theodore (2018) suggest administering generics instead of brand name ASMs when an ASM is first started, to prevent confusion among patients.

Similarly, Kesselheim and colleagues (2013) conducted a case control study that examined adherence to ASMs in the setting of changes in appearance and color. Specifically, the study looked at cases where patients became nonpersistent, defined as someone "failing to refill a prescription within 5 days of the elapsed days supplied." Findings showed that changes in pill color specifically had a significant effect on the odds of nonadherence to ASMs (Kesselheim et al., 2013).

In the Equivalence Among Generic Antiepileptic Drugs study, Privitera and colleagues (2016) introduce the idea of the nocebo effect, defined as a situation where "an inert substance produces a perceived negative effect, or in this case, an equivalent substance produces a perceived less potent therapeutic effect or new adverse effect. Because patients and clinicians expect the generic products to be inferior, the therapeutic effect is assumed to be reduced." Essentially, the concept of the nocebo effect is the opposite of the placebo effect. So, if a patient expects to have a negative experience after starting a new generic ASM, this results in the treatment having a more negative effect (Privitera et al., 2016).

However, there are a substantial number of reports and review articles by professional neurologists that indicate issues with generic ASMs, such as increased risk of seizures, inadequate seizure control, and adherence issues. It is likely that there are lots of anecdotal or anonymous patient reports of seizures, many often not reported to the FDA or published in journals.

As such, prior to switching, physicians should have discussions with their patients to watch for breakthrough seizures or other adverse effects. Additionally, to help prevent the problems associated with generic ASM switching, providers must provide proper patient education on what to expect to increase adherence when switching between brand name to generics or between generics. This includes explaining differences in medication appearance so that patients know what to expect when they switch medications. This raises the question of how these providers can provide educational materials in a way that will be most beneficial to patients.

A study by Hohmann et al. (2019) examined the opinions of patients and their caregivers regarding the use of FDA-

developed educational materials as they pertain to generic drugs. Their findings identified a set of needs to increase receptiveness regarding educational material about generic drugs. Study participants identified all of the following as educational needs: (1) modernized graphics; (2) emphasis on generic cost-saving for consumers; (3) reduction of scare tactics when discussing adverse events; (4) dissemination of information directly from physicians and pharmacies (Hohmann et al., 2019).

Overall, based on the published evidence on specific generic ASMs, it is imperative that physicians and pharmacists provide proper patient education on what they can expect when switching from a brand name to a generic or when switching between generics. Another suggestion would be to consider that all such ASMs be considered for inclusion in NTI class to prevent the clinical outcome issues associated with generic ASM switching.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Elmer, Reddy.

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